

HOW GOES THE WAR AGAINST ANTIBIOTIC RESISTANCE?

Robert A. Weinstein, MD
March 24, 2016
Rush University Medical Center
Cook County Health & Hospitals System

Disclosures: Sage Inc (Remote) & CDC (Current) Funding

18 Threats Highlighted for United States

Urgent Threats
■ <i>Clostridium difficile</i>
■ Carbapenem-resistant Enterobacteriaceae (CRE)
■ Drug-resistant <i>Neisseria gonorrhoeae</i>
Serious Threats
■ Multidrug-resistant <i>Acinetobacter</i>
■ Drug-resistant <i>Campylobacter</i>
■ Fluconazole-resistant <i>Candida</i> (a fungus)
■ Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs)
■ Vancomycin-resistant <i>Enterococcus</i> (VRE)
■ Multidrug-resistant <i>Pseudomonas aeruginosa</i>
■ Drug-resistant Non-typhoidal <i>Salmonella</i>
■ Drug-resistant <i>Salmonella</i> Typhi
■ Drug-resistant <i>Shigella</i>
■ Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)
■ Drug-resistant <i>Streptococcus pneumoniae</i>
■ Drug-resistant tuberculosis
Concerning Threats
■ Vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA)
■ Erythromycin-resistant Group A <i>Streptococcus</i>
■ Clindamycin-resistant Group B <i>Streptococcus</i>

<http://www.cdc.gov/drugresistance/threat-report-2013/>

THE ISSUES

- Dimensions & Drivers of the Problem
- Dimensions of the Response
- Are Solutions Likely?
 - Achieved
 - Achievable
 - Aspirational

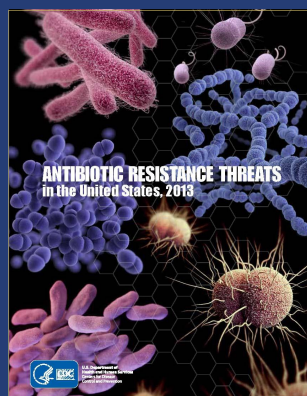
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least  **2,049,442** illnesses,
 **23,000** deaths

*bacteria and fungus included in this report

<http://www.cdc.gov/drugresistance/threat-report-2013/>

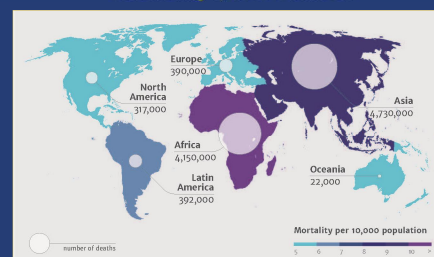
THE PROBLEM



<http://www.cdc.gov/drugresistance/threat-report-2013/>

GLOBAL DIMENSIONS

Estimate: By 2050, 10 Million Deaths Attributed to AMR Every Year Costing World Economy \$100 Trillion



Review on Antimicrobial Resistance (AMR), 2014. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London, UK <http://amr-review.org>

DRIVER 1: PROFLIGATE ANTIBIOTIC USE

Over-the-Counter Sales of Antibiotics and Injectables, by Income Group

Country Income Group (number of countries)											
		Low (36)	Lower-middle (53)	Upper-middle (56)	High (52)	Global Total (197)					
% there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant+Alexander Fleming, Nobel Lecture, December 11, 1945											
Substitution in private sector facilities is allowed	Total	34	85.3%	42	77.1%	45	69.6%	42	78.6%	170	77.1%
	Yes	31		43		34		12		120	
Antibiotics are sometimes sold over-the-counter without a prescription	Total	24	91.2%	45	89.6%	45	73.9%	39	30.8%	167	71.9%
	Yes	31		35		24		8		101	
Injectables are sometimes sold over-the-counter without a prescription	Total	34	91.2%	47	80.9%	43	55.8%	38	21.1%	162	62.3%
	Yes	31		35		24		8		101	

Source: Pharmaceutical Sector Country Profiles, 2013; WHO

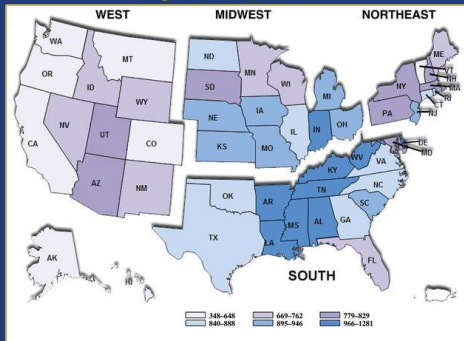
DRIVER 2: THE ENVIRONMENT



China's lakes of pig manure spawn antibiotic resistance

Larson, Science 2015; 347(6223):704

Antibiotic Prescriptions per 1,000 Persons by State, 2011



Hicks et al, Clin Infect Dis 2015; 60:1308-16

High Income Urban Breeding Grounds?

Geospatial Resolution of Human and Bacterial Diversity with City-Scale Metagenomics

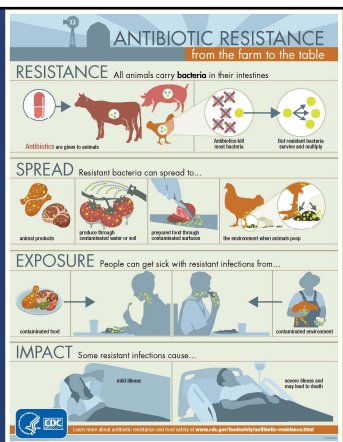
Elorhien Afshinnekoo,^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000}

- This is a city-s system. public
- Almost half of known organi
- Hundreds of s riders bring m
- One station fl environment
- Human allele



Afshinnekoo et al, CELS 2015; <http://dx.doi.org/10.1016/j.cels.2015.01.001>

The 800 lb Heifer in the Room: The Role of Antimicrobials in Animal Husbandry as a Resistance Driver?



DRIVER 3: NATURE

Resistance Genes — A Feature of the Human Microbiome

The microbiome of uncontacted Amerindians

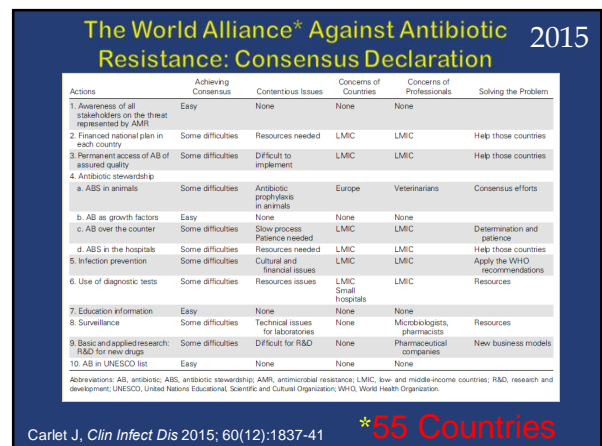
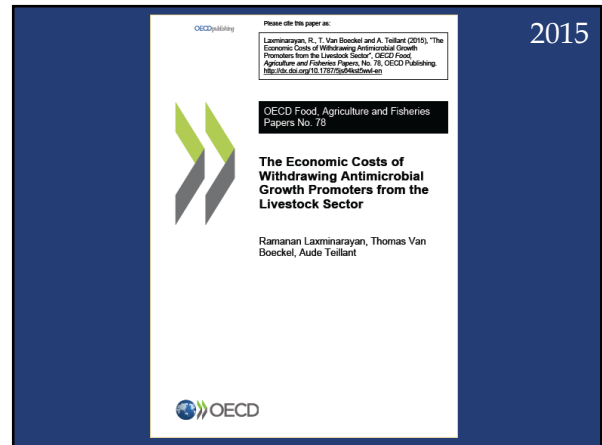
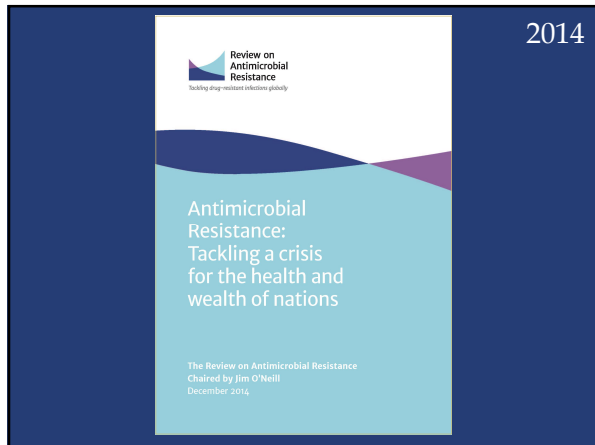
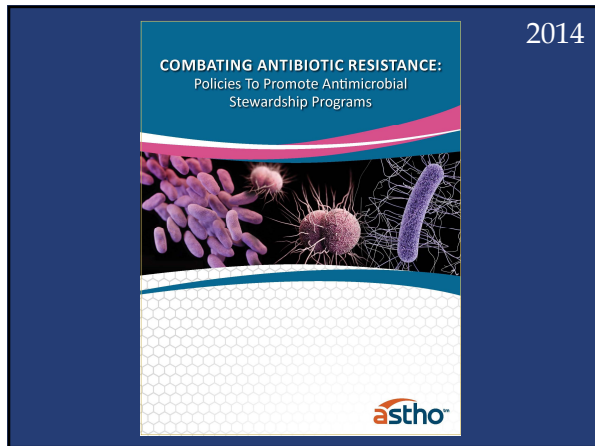
Jose C. Clemente,^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000}

Despite their isolation, presumably for >11,000 years since their ancestors arrived in South America, and no known exposure to antibiotics, they harbor bacteria that carry functional antibiotic resistance (AR) genes, including those that confer resistance to synthetic antibiotics and are syntenic with mobilization elements. These results suggest that Westernization significantly affects human microbiome diversity and that functional AR genes appear to be a feature of the human microbiome even in the absence of exposure to commercial antibiotics.



Clemente et al, Sci Adv 2015;1:e1500183







National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan) Charter

Executive Order 13676 directs the Secretary of Health and Human Services (Secretary) to establish the Advisory Council in consultation with the Secretaries of Defense and Agriculture. The Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of Executive Order 13676, including the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the [National Action Plan for Combating Antibiotic-Resistant Bacteria \(Action Plan\)](#). The Advisory Council shall function solely for advisory purposes.

www.hhs.gov/ash/cab/

PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

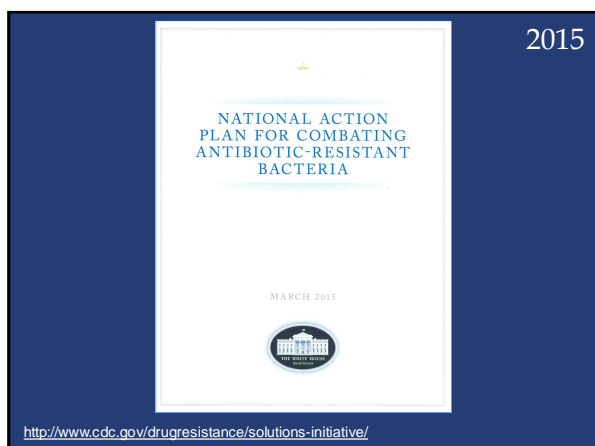


Charge

National Strategy for Combating Antibiotic-Resistant Bacteria
Goals of National Action Plan:

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
2. Strengthen National One-Health Surveillance Efforts to Combat Resistance
3. Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
5. Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA



Membership

- 15 Voting Members; 5 Non-Voting Organizational Liaisons; 10 Non-Voting Ex Officios
- Dr. Martin Blaser (Chair)
 - Dr. Lonnie King (Vice Chair)
 - Dr. Bruce Gellin (Designated Federal Officer)



PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Current Working Groups (WGs)

Developed WGs based on the 5 National Action Plan goals:

1. Antibiotic Stewardship: Human and animal
2. One-Health Surveillance: Animal, environment, human
3. Diagnostic Innovations: Fast, accurate, inexpensive
4. Research, Treatment, and Control R&D: Drug, alternatives, vaccines
5. International Collaboration on CARB: Microbes don't respect borders

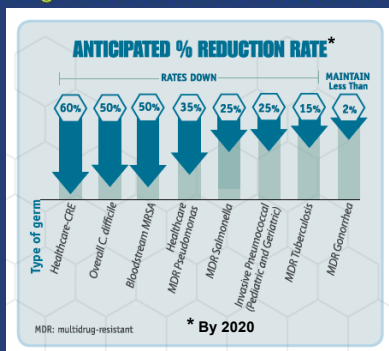
WG findings to be presented at the upcoming **March 30-31, 2016**, public meeting in Washington, DC. Visit www.hhs.gov/ash/carb

PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Improved Chances of Success — What's Different Now?

- Higher-level Political Will
- Continuing Infection Control Refinements
- Renewed Focus on Antimicrobial Stewardship
- Dramatic Informatics Abilities
- Striking Advanced Molecular Diagnostics
- Major Microbiome Insights

Combating Antibiotic-Resistant Bacteria: Goals



<http://www.cdc.gov/drugresistance/solutions-initiative/>

THE ISSUES

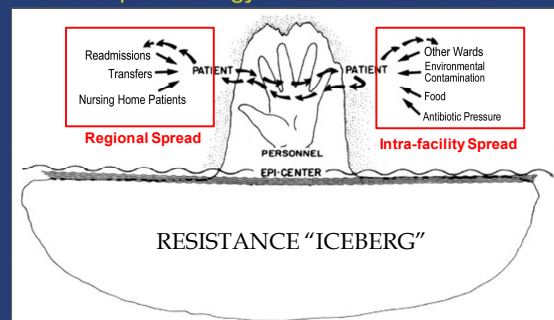
- Dimensions & Drivers of the Problem
- Dimensions of the Response
- Are Solutions Likely?
 - Achieved (4)
 - Achievable
 - Aspirational

A Skeptical View

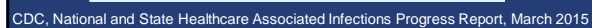
When the situation was manageable it was neglected, and now that it is thoroughly out of hand we apply too late the remedies which then might have effected a cure. There is nothing new in the story — it falls into the confirmed unteachability of mankind. Want of foresight, unwillingness to act when action would be simple and effective, lack of clear thinking, confusion of counsel until the emergency comes — these are the features which constitute the endless repetition of history.

Winston Churchill
Speech -- Air Parity Lost
May 2, 1935
British House of Commons

ACHIEVED 1: Much Epidemiology of Resistance Is Known



Adapted from Weinstein & Kabins, *Am J Med* 1981; 70:449-54

Huang et al, *N Engl J Med* 2013; 368(24):2255-65

MMWR March 4, 2011; 60(8):243

LTACH, Long-term acute care hospital;
CRE, Carbapenem-resistant *Enterobacteriaceae*
See Hayden MK et al, *Clin Infect Dis* 2015; 60(8):1153-61

MDRO, Multi-drug resistant organism; GI, Gastrointestinal

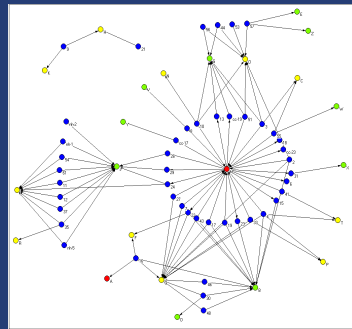
8

Emergence & Rapid Regional Spread of *K pneumoniae* Carbapenemase-Producing Enterobacteriaceae HOSPITAL AND LONG-TERM CARE INTERRELATIONS

Social Network
depiction of LTACH,
Nursing Home, &
Hospital spread of KPC
(Carbapenem-resistant
Klebsiella pneumoniae)

Legend
● LTACH
● Nursing Home
● Acute Hospital
● Patient

LTACH, Long term acute
care hospital; MDRO,
Multidrug resistant
organism



Won et al, *Clin Infect Dis* 2011; 53(6):532-40

XDRO registry
www.XDRO.org for Illinois

Extensively drug resistant organism registry

Carbapenem-resistant Enterobacteriaceae (CRE) are extremely drug resistant organisms (XDRs) that have few treatment options and high mortality rates. CRE are increasingly detected among patients in Illinois, including acute and long term care healthcare facilities.

In response to the CRE public health threat, the Illinois Department of Public Health (IDPH) has guided development an infection control tool called the XDRO registry. The purpose of the XDRO registry is two-fold:

1. **Improve CRE surveillance:** The first CRE-positive culture per patient stay must be reported to the XDRO registry.
2. **Improve inter-facility communication:** Healthcare facilities can query the XDRO registry to see whether a patient has been previously reported as CRE-positive.

For access to the XDRO registry, click [here](#)

UPDATES

IL CRE Detect and Protect Campaign. [More...](#)

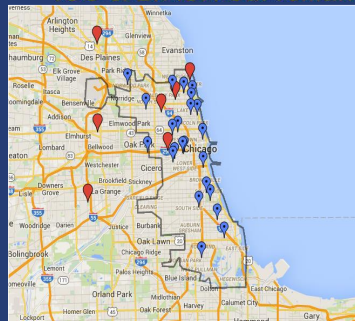
CRE are reportable to IDPH via the XDRO registry. Links: [\[IDPH letter to facilities, September 2013\]](#) [\[reporting rule\]](#)

XDRO registry orientation webinar [\[slides\]](#) [\[recording\]](#)

CDC guidance on control of CRE: [\[The 2012 Toolkit\]](#)

The XDRO registry is a product of collaboration between IDPH, Medical Research Analytic and Informatics [\[www.MRAI.us\]](#) and [\[www.XDRO.org\]](#)

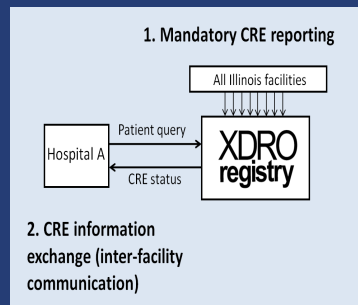
REALM Project – ICU & LTACH Surveillance for KPC



Hospital ICUs (blue)
LTACHs (red)

REALM, Regional Evaluation of Legislative Mandate to screen patients for MRSA; LTACH, Long-term acute care hospital; KPC, *Klebsiella pneumoniae* carbapenemase producers

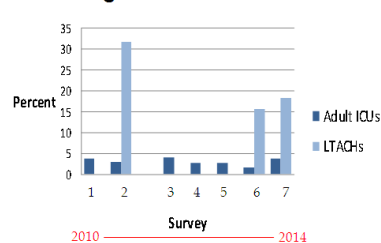
XDRO Registry Overview



Participants: Illinois hospitals including LTACHs, nursing homes, laboratories

See: www.xdro.org

Prevalence of KPC Colonization among ICU vs. LTACH Patients



KPC, *Klebsiella pneumoniae* carbapenemase producers; ICU, Intensive Care Unit; LTACH, long-term acute care hospital

REALM data courtesy of Michael Lin, MD, MPH; unpublished data, not for distribution

Alert Anecdote: IP Testimonial

"...I got a CRE alert last night on a patient we've never had before... the patient is from a nursing home... I went to check his transfer notes... nothing is in there. I don't even think the nursing home knows that he has CRE. It was **very exciting** this morning to get this one because it was a case we didn't know about... I really, really think this will be a cool system..."

CRE, Carbapenem-resistant *Enterobacteriaceae*

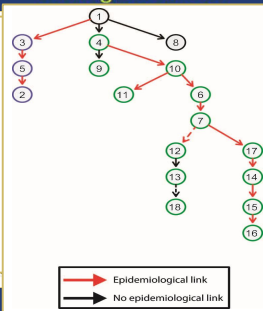
ACHIEVABLE 2: HARNESS MOLECULAR GENETICS

Putative map of *K. pneumoniae* Transmission During Outbreak

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae*

Evan S. Snitkin,¹ Adrian NISC Comparative Sequencing,² Tara N. Palmore,³ Julie

The Gram-negative bacteria *Klebsiella pneumoniae* is a leading cause of hospital-acquired infection. Infection with carbapenem-resistant *K. pneumoniae* is particularly concerning because of the limited treatment options available. We performed whole-genome sequencing on isolates from an outbreak of carbapenem-resistant *K. pneumoniae* to determine the source and spread of the infection.

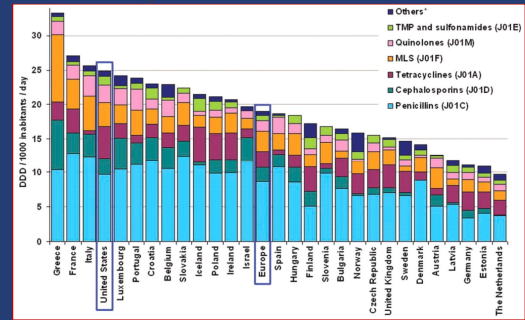


Carbapenem-Resistant Sequencing

ions, primarily among limited few treatment options, the Center experienced an outbreak of carbapenem-resistant *K. pneumoniae*. Whole-genome sequencing was performed on isolates from the outbreak to determine the source and spread of the infection. The analysis traced the outbreak to three independent cases, with subsequent transmission occurring through the hospital. Our analysis demonstrates the utility of whole-genome sequencing in identifying and controlling outbreaks of carbapenem-resistant *K. pneumoniae*.

Snitkin et al, *Sci Transl Med* 2012; <http://stm.sciencemag.org/content/4/148/148ra116.full.html>

Total Outpatient Antibacterial Use*



*In the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy).

Goossens et al, *Clin Infect Dis* 2007;44:1091-5 and 1259

ACHIEVABLE 3: IMPROVE ANTIMICROBIAL STEWARDSHIP

Centers for Disease Control and Prevention

MMWR
Weekly / Vol. 63 / No. 9

Morbidity and Mortality Weekly Report

March 7, 2014

Vital Signs: Improving Antibiotic Use Among Hospitalized Patients

Sam Fackler, MD¹, James Duggan, PhD¹, Susan Dugas, MD¹, Shelley Magill, MD, PhD², Lori A. Peltz, MD³, Paul Magallon, MPH¹, Rachel Hays, PhD¹, Kara Shalek, PhD¹, Michael A. Bell, PhD¹, Michael J. Tenover, MD¹, Michael H. Tenover, MD¹, Oliver Dauter, MD¹, Elizabeth Chabot-Holmes, PhD¹, James M. Maki, MD¹, Kimberly Tenover-Hicks, MPH¹, John Jorgens, MD¹, Nadia Shalek, PhD¹, Ron Brown, Jr., PhD¹, David McQuinn, MD¹, Amy Skarlat, MPH¹, Susan Thompson, MD¹ (for the authors and all co-authors)

On March 6, 2014, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

Background: Antibiotics are essential to effectively treat many hospitalized patients. However, when antibiotics are prescribed inappropriately, they can harm patients and potentially expose them to risks for complications, including *Clostridium difficile* infection (CDI) and antibiotic-resistant infections. Information is needed on the frequency of inpatient antibiotic prescribing in hospitals and how improved prescribing will benefit patients.

Methods: A national administrative database (MarketScan Hospital Drug Database) and CDC's Emerging Infections Program (EIP) data were analyzed to assess the potential for improvement of inpatient antibiotic prescribing. Variability in days of therapy for selected antibiotics reported to the National Healthcare Safety Network (NHSN) antimicrobial use system was compared. The impact of reducing inpatient antibiotic exposure on incidence of CDI was modeled using data from two U.S. hospitals.

Results: In 2010, 55,796 of patients discharged from 323 hospitals received antibiotics during their hospitalization. EIP system data from 183 hospitals in 2010 describe inpatient antibiotic use. Antibiotic prescribing primarily could be improved in 77.2% of the most common prescription scenarios reviewed. There were identified differences in usage rates among 26 medical/surgical wards reporting to NHSN. Models estimate that the total direct and indirect effects from a 30% reduction in use of broad-spectrum antibiotics will result in a 20% reduction in CDI.

Conclusions: Antibiotic prescribing for inpatients is common, and there is ample opportunity to improve use and patient safety by reducing inpatient antibiotic prescribing.

Implications for Public Health: Hospital administrators and health-care providers can reduce potential harm and risk for antibiotic resistance by implementing formal programs to improve antibiotic prescribing in hospitals.

Frickin et al, *MMWR* March 7, 2014; 63(9):194

Stewardship and Antibiotic Use for In-patients

- Seven Stewardship Core Elements Proposed → CMS Mandate
- Comprehensive Surveillance for Antibiotic Use (AU) is Essential
- NHSN 2015 Survey of ~4,000 U.S. Hospitals will Provide Details of Stewardship Programs
- Need to Engage Long-term Care Facilities

NHSN, National Healthcare Safety Network; NQF, National Quality Forum; CMS, Centers for Medicare & Medicaid Services
<http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>



Example of Plans for Reducing Out-patient Antibiotic Prescribing

- Establish antibiotic prescribing patterns by age, diagnosis, and antibiotic choice
- Reach consensus on appropriate goals for reductions in use for common infections
- Engage stakeholders, promote goals, and track progress
- Now "Global-ize"?

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases



Computer Facilitated Prescribing

A COMPUTER-ASSISTED MANAGEMENT PROGRAM FOR ANTIBIOTICS AND OTHER ANTIINFECTIVE AGENTS

R. SCOTT EVANS, Ph.D., STANLEY L. PIETROTTI, M.S., R.Ph., DAVID C. CLASSEN, M.D., M.S., TERRY F. CLEMMER, M.D., LINDA K. WEAVER, M.D., JAMES F. GRINE, JR., M.D., JAMES F. LLOYD, B.S., AND JOHN P. BURKE, M.D.

When Doctors Followed Computer-driven Recommendations for Antibiotic Therapy

Shorter Hospital Stays: 10 days vs 17 days ($p < 0.001$)

Lower Costs per stay: \$26,000 vs \$45,000 ($p < 0.001$)

processes and outcomes were compared with those for the 1136 patients admitted to the same unit during the two years before the intervention period. The use of the program led to significant reductions in orders for drugs to which the patients had reported

adjusted mean, 10.0 vs. 16.0 and 14.3 days, $P < 0.001$. **Conclusions:** A computerized antimicrobials-management program can improve the quality of patient care and reduce costs. (N Engl J Med 1998;338:232-8.)

Evans et al, *N Engl J Med* 1998; 338(4):232-8

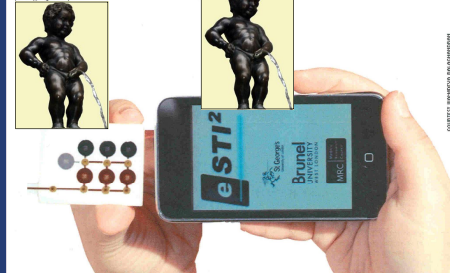
Some Challenges for Antimicrobial Stewardship: What Prescribers Say

- Antimicrobial Stewardship takes too much time, which affects our productivity
- Antimicrobial Stewardship risks unhappy patients, which affects our income
- Lessening antibiotic use in animal husbandry is still largely voluntary, which annoys many doctors who say, "Don't bother us until that bigger problem is solved"

ASPIRATION 1: Ultimate Need: Rapid Clinic or Bedside Diagnosis

eSTI2 project looks to develop blood testing chip for mobile devices

The mobile industry is making its way into a ton of fields and one area that it is becoming more and more influential is the medical field. From tablet implementation in hospitals to scheduling appointments online, mobile tech is looking to explode in the field. One of the biggest ideas getting a huge financial bump today is the eSTI2 project, which has received a four-year grant from the UK's Medical Research Council to develop a chip that could make blood testing



ACHIEVABLE 4: FOOL-PROOF DEVICES A Basic Question for Device-related Infections – Technologic Fixes?

Do We Need Technology to Trump Bad Behavior?

Change human behavior
(e.g., improve attention to hygiene and asepsis)

or

Design a more "fool-proof" device. . . ?

LONGITUDE PRIZE

How can I get involved?
Antibiotic resistance affects us all - find out more.



Prize View Entries Blog The Challenge About us Contact us

UK's Longitude Prize in Antibiotic Resistance

LONGITUDE PRIZE OPEN

Longitude Prize is a challenge with a £10 million prize fund to help solve the problem of global antibiotic resistance. It is being run by Nesta, supported by Innovate UK, the new name for the Technology Strategy Board, as funding partner.

- Longitude Prize is a £10 million challenge
- Public decided the focus of the new prize to be antibiotic resistance
- The 5-year race has begun to develop a point-of-care test that will identify when antibiotics are needed and - if they are - which ones to use
- Prize is the largest UK challenge and the first prize of its kind to be determined through a public vote
- As of Aug 5, 2015 - 92 teams from 15 countries have registered

THE ISSUES

- Dimensions & Drivers of the Problem
- Dimensions of the Response
- Are Solutions Likely?
 - Achieved
 - Achievable
 - Aspirational (3)

Federal Register / Vol. 80, No. 105

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health


Announcement for Request for Comment for: Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge

Authority: 15 U.S.C. 3719

SUMMARY: The U.S. Department of Health and Human Services (HHS) intends to hold a prize competition in which up to \$20 million will be made available, subject to the availability of funds, for the delivery of one or more successful rapid point-of-care diagnostics that may be used by health care providers to identify bacterial infections.

Submission Period begins June 2, 2015, 9:00 a.m. EST. Submission Period ends 5 p.m. EST July 17, 2015.

ASPIRATION 2: "New" Approaches to Treat Infections?



What Did Martin Arrowsmith, MD Discover?

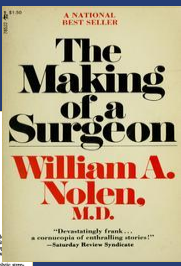
SHORT-TERM
New Antibiotics

LONG-TERM
New Approaches?

ASPIRATION 3: Microbiome Manipulation to Control A Reservoir of Resistance?

Use of Bacterial Interference to Control a Staphylococcal Nursery Outbreak

Abnormal Colonization of Neonates in an ICU: Conversion to Normal Colonization by Pharyngeal Implantation of Alpha Hemolytic Streptococcus Strain 215



Light et al, *Am J Dis Child* 1967; 113:291
Sprunt et al, *Pediatr Res* 1980; 14:308

Maybe New Antibiotics Aren't Enough?

DRUG RESISTANCE

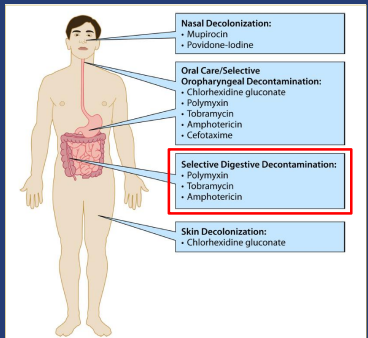
Fitness cost of antibiotic susceptibility during bacterial infection

Damien Roux,^{1,2,3,*} Olga Danilchanka,^{4,*} Thomas Guillard,^{1,5,*} Vincent Cattoir,^{1,6,*} Hugues Aschard,⁷ Yang Fu,⁸ Francois Angoulvant,⁹ Jonathan Messika,² Jean-Damien Ricard,² John J. Mekalanos,⁸ Stephen Lory,⁴ Gerald B. Pier,^{1*} David Skurnik^{1*}

- The increased virulence of antibiotic-resistant strains in experimental settings raises a serious concern that drug-resistant strains might be better fit to cause serious, more difficult to treat infections
- Overall... (such) strains... could have serious clinical consequences beyond the difficulties in choosing an effective therapeutic treatment

Roux et al, *Sci Transl Med* 2015; 9(297)
Available at: <http://stm.sciencemag.org/content/7/297/297ra114>

Recognized Decolonization Strategies to Prevent Health Care-associated Infections



- Nasal Decolonization:**
 - Mupirocin
 - Povidone-iodine
- Oral Care/Selective Oropharyngeal Decontamination:**
 - Chlorhexidine gluconate
 - Polymyxin
 - Tobramycin
 - Amphotericin
 - Cefotaxime
- Selective Digestive Decontamination:**
 - Polymyxin
 - Tobramycin
 - Amphotericin
- Skin Decolonization:**
 - Chlorhexidine gluconate

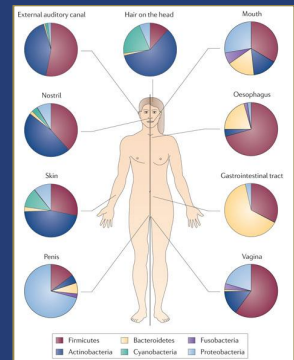
Septimus & Schweizer, *Clin Microbiol Rev* 2016; 29:201-2

Targets Currently Uncontrolled by Vaccination

Diseases and infections with commonly used vaccines	Diseases and infections with no vaccine or only partially effective vaccines
Poliovirus	Leishmaniasis
Diphtheria/tetanus type 5	Cholera
Hepatitis type 4	Measles
Hepatitis type 6	Scarlet fever
Scarlet fever type 1	Scarlet fever type 2
Scarlet fever type 3	Scarlet fever type 4
Scarlet fever type 4	Scarlet fever type 5
Scarlet fever type 5	Scarlet fever type 6
Scarlet fever type 6	Scarlet fever type 7
Scarlet fever type 7	Scarlet fever type 8
Scarlet fever type 8	Scarlet fever type 9
Scarlet fever type 9	Scarlet fever type 10
Scarlet fever type 10	Scarlet fever type 11
Scarlet fever type 11	Scarlet fever type 12
Scarlet fever type 12	Scarlet fever type 13
Scarlet fever type 13	Scarlet fever type 14
Scarlet fever type 14	Scarlet fever type 15
Scarlet fever type 15	Scarlet fever type 16
Scarlet fever type 16	Scarlet fever type 17
Scarlet fever type 17	Scarlet fever type 18
Scarlet fever type 18	Scarlet fever type 19
Scarlet fever type 19	Scarlet fever type 20
Scarlet fever type 20	Scarlet fever type 21
Scarlet fever type 21	Scarlet fever type 22
Scarlet fever type 22	Scarlet fever type 23
Scarlet fever type 23	Scarlet fever type 24
Scarlet fever type 24	Scarlet fever type 25
Scarlet fever type 25	Scarlet fever type 26
Scarlet fever type 26	Scarlet fever type 27
Scarlet fever type 27	Scarlet fever type 28
Scarlet fever type 28	Scarlet fever type 29
Scarlet fever type 29	Scarlet fever type 30
Scarlet fever type 30	Scarlet fever type 31
Scarlet fever type 31	Scarlet fever type 32
Scarlet fever type 32	Scarlet fever type 33
Scarlet fever type 33	Scarlet fever type 34
Scarlet fever type 34	Scarlet fever type 35
Scarlet fever type 35	Scarlet fever type 36
Scarlet fever type 36	Scarlet fever type 37
Scarlet fever type 37	Scarlet fever type 38
Scarlet fever type 38	Scarlet fever type 39
Scarlet fever type 39	Scarlet fever type 40
Scarlet fever type 40	Scarlet fever type 41
Scarlet fever type 41	Scarlet fever type 42
Scarlet fever type 42	Scarlet fever type 43
Scarlet fever type 43	Scarlet fever type 44
Scarlet fever type 44	Scarlet fever type 45
Scarlet fever type 45	Scarlet fever type 46
Scarlet fever type 46	Scarlet fever type 47
Scarlet fever type 47	Scarlet fever type 48
Scarlet fever type 48	Scarlet fever type 49
Scarlet fever type 49	Scarlet fever type 50
Scarlet fever type 50	Scarlet fever type 51
Scarlet fever type 51	Scarlet fever type 52
Scarlet fever type 52	Scarlet fever type 53
Scarlet fever type 53	Scarlet fever type 54
Scarlet fever type 54	Scarlet fever type 55
Scarlet fever type 55	Scarlet fever type 56
Scarlet fever type 56	Scarlet fever type 57
Scarlet fever type 57	Scarlet fever type 58
Scarlet fever type 58	Scarlet fever type 59
Scarlet fever type 59	Scarlet fever type 60
Scarlet fever type 60	Scarlet fever type 61
Scarlet fever type 61	Scarlet fever type 62
Scarlet fever type 62	Scarlet fever type 63
Scarlet fever type 63	Scarlet fever type 64
Scarlet fever type 64	Scarlet fever type 65
Scarlet fever type 65	Scarlet fever type 66
Scarlet fever type 66	Scarlet fever type 67
Scarlet fever type 67	Scarlet fever type 68
Scarlet fever type 68	Scarlet fever type 69
Scarlet fever type 69	Scarlet fever type 70
Scarlet fever type 70	Scarlet fever type 71
Scarlet fever type 71	Scarlet fever type 72
Scarlet fever type 72	Scarlet fever type 73
Scarlet fever type 73	Scarlet fever type 74
Scarlet fever type 74	Scarlet fever type 75
Scarlet fever type 75	Scarlet fever type 76
Scarlet fever type 76	Scarlet fever type 77
Scarlet fever type 77	Scarlet fever type 78
Scarlet fever type 78	Scarlet fever type 79
Scarlet fever type 79	Scarlet fever type 80
Scarlet fever type 80	Scarlet fever type 81
Scarlet fever type 81	Scarlet fever type 82
Scarlet fever type 82	Scarlet fever type 83
Scarlet fever type 83	Scarlet fever type 84
Scarlet fever type 84	Scarlet fever type 85
Scarlet fever type 85	Scarlet fever type 86
Scarlet fever type 86	Scarlet fever type 87
Scarlet fever type 87	Scarlet fever type 88
Scarlet fever type 88	Scarlet fever type 89
Scarlet fever type 89	Scarlet fever type 90
Scarlet fever type 90	Scarlet fever type 91
Scarlet fever type 91	Scarlet fever type 92
Scarlet fever type 92	Scarlet fever type 93
Scarlet fever type 93	Scarlet fever type 94
Scarlet fever type 94	Scarlet fever type 95
Scarlet fever type 95	Scarlet fever type 96
Scarlet fever type 96	Scarlet fever type 97
Scarlet fever type 97	Scarlet fever type 98
Scarlet fever type 98	Scarlet fever type 99
Scarlet fever type 99	Scarlet fever type 100

Plotkin et al, *N Engl J Med* 2015; 373:297-300

NIH Human Microbiome Project

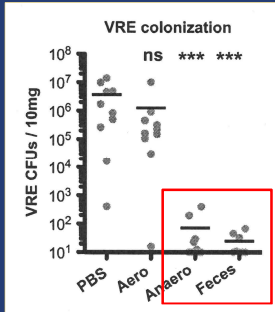


WE ARE WHAT WE EAT?

- Gut Microbiomes of Malawian Twins Discordant for Kwashiorkor, *Science* 2013; 339:548-54
- Antibiotics Treat Malnutrition? *N Engl J Med* 2013; 368:425-35
- Intestinal Metabolism and Cardiac Risk, *N Engl J Med* 2013; 368:1575-84
- Gut Microbiota in Diabetes, *Nature* 2012; 490:55-60
- Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*, *N Engl J Med* 2013; 368:407-15

Spor, Koren, Ley, *Nature Rev Microbiol* 2011; 9:279

Commensal Anaerobic Bacteria Suppress VRE Colonization in Antibiotic-treated Mice



Mice were infected with 10⁸ VRE CFU after 1 week of ampicillin treatment. One day after infection, ampicillin treatment was stopped. Mice were orally gavaged for 3 consecutive days, starting 1 day after antibiotic cessation, with PBS, a suspension of fecal pellets from untreated mice (feces), or an aerobic (aero) or anaerobic (anaero) culture of fecal microbiota from untreated mice. Numbers of VRE CFU in the fecal pellets of infected mice were analyzed 5 weeks after infection (*n* 8 to 10). Limit of detection, 10 CFU/10 mg. ***, significantly different (*P* < 0.001) from the PBS group; ns, not significant.

Ubada et al, *Infect Immun* 2013; 81(3):965-73

CONCLUSIONS

- Now is the time or never at all to control antimicrobial resistance; much is already known that can be harnessed
- This war — like all wars — will require money, will power, resources, & ingenuity
- Globalization of effort — especially to lessen environmental risk & to improve antimicrobial use — is essential and will require Olympian levels of partnership



Thank you!